Remarks/Arguments

Claims 22 to 49 are pending. Claim 21 has been cancelled. Claims 1 to 20 were previously cancelled. Claims 22, 24 to 27, 30, 37, 40 and 45 to 49 have been amended to correct minor formal errors in the chemical names, etc. Claim 22 has been amended to recite that the conversion (intermediate) product of the reduction step is used without isolation in the subsequent reaction step. Support for the amendment to Claim 22 is found in the wording of Claim 37 and on page 4, lines 1 to 6, of the English language translation of the specification (i.e., page 3, line 30, and page 4, lines 4 to 6, of the published PCT application). Claim 22 is a direct embodiment of Example 3b.

Before dealing with the Section 102 rejection and two of the Section 103(a) rejections, applicants have established hereafter the basis for asserting that the underlying rejection references are not prior art under the statute.

This application is a national stage application of International Application No. PCT/EP00/00240 so the time limit in 37 C.F.R. 1.55 (a)(1)(i) to file the claim for priority does not apply to this application.

Rule 1.55(a) states:

> "(a) An applicant in a nonprovisional application may claim the benefit of the filing date of one or more prior foreign applications under the conditions specified in 35 U.S.C. 119(a) through (d) and (f), 172, and 365(a) and (b)."

Rule 1.55(a)(1)(ii) states:

"(ii) In an application that entered the national stage from an international application after compliance with 35 U.S.C. 371, the claim for priority must be made during the pendency of the application and within the time limit set forth in the PCT and the Regulations under the PCT."

Claim for benefit of European Patent Application No. 99100590.1 (filed on January 14, 1999) is expressly stated in the executed filed declarations of each of the six joint inventors. The following is a quotation of the claim for priority found in all six individual declarations:

"I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(b) of any foreign application(s) for parent, inventor's or plant breeder's rights certificate(s), or 365(a) of any PCT international application which designated at least one country other than the Untied States of America, listed below and have also identified below, by checking the box, any foreign application for patent, inventor's or plant breeder's rights certificate(s), or any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached Yes or No
99100590.1	Europe	01/14/1999		X
PCT/EP00/00240	International	01/13/2000		X"

Applicants have clearly made claim for priority of such European application (and PCT application).

The unexecuted declaration filed on July 16, 2001 claims priority benefit of European Application No. 99100590.1, and claims benefit of U.S. Provisional Application 60/145,996.

The Office Action Summary page of the Office Action acknowledged the claim for foreign priority and receipt of certified copies of the priority documents. (Note that the Examiner should have mark the box that copies of the certified copies had been received from the International Bureau.)

The official Filing Receipt (mailed March 9, 2005) states:

"**Domestic Priority data as claimed by applicant**

This application is a 371 of PCT/EP00/00240 01/13/2000 which claims benefit of 60/145,996 07/29/1999

Foreign Applications

EUROPEAN PATENT OFFICE (EPO) 00100590.1 01/14/1999"

Enclosed is a copy of the cover page of WO 00/42014 (published version of applicants' PCT application). Note that it lists EP 99100590.1, filed on January 14, 1999, and US 60/145,996, filed on July 29, 1999, as priority documents.

Rule 1.55(a)(4)(i) states:

"(4)(i) An English language translation of a non-English language foreign application is not required except:

***

(B) When necessary to overcome the date of a reference relied upon by the examiner, or

***."

An English-language translation of US 60/145,996 is enclosed with a statement by a translator that it is an accurate English language translation thereof.

This application already contains an English-language translation of PCT/EP00/00240 (WO 00/42014) and a statement that such is an accurate English-language translation of such PCT application.

There is also an English-language translation, and the required accuracy statement, in U.S. Provisional Application 60/145,996.

The Office Action stated that the following is a quotation of the appropriate paragraphs 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless—
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 21 has been rejected under 35 U.S.C. 102(b) as being anticipated by Bessard et al. (U.S. Patent No. 6,600,046). Applicants traverse this rejection.

The earliest date that Bessard et al. has under Section 102/Section 102(e) is March 3, 2000, that is the U.S. filing date of the Bessard et al. U.S. Provisional Application. As shown above, applicants have benefit of three earlier foreign, PCT and domestic priority dates, namely, (1) European Patent Application No. 99100590.1, filed January 14, 1999, (2) U.S. Provisional Application 60/145,996, filed on July 29, 1999, and (3) International Application No. PCT/EP00/00240, filed on January 13, 2000. Therefore, Bessard et al. is not prior art against any of

applicants' claims including Claim 21. However, Claim 21 has been cancelled because of references cited in the International Search Report.

The Office Action stated that Bessard et al. teach the claimed 6-methylpyridine-3-yl)-2-[4-(methylsufonyl)phenyl]ethanone as claimed; and see, for example, column 1 lines 12 to 26. What Bessard et al. teaches is not relevant because Bessard, et al. is not prior art to any of applicants' claims. Reference is made to the Hilmer doctrine.

This rejection should be withdrawn.

The Office Action stated that the following is quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 21 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Pye et al. (WO 98/47871). Applicants have cancelled Claim 21 so this obviousness rejection is not relevant.

However, applicants point out that this obviousness rejection is defective and does not follow Patent Office policy. The Examiner has not factually established in the record a prima facie showing of obviousness of any of

applicants' claims. The Examiner also has not factually established in the record the level of skill of one ordinarily skilled in the art, without which this obviousness rejection is defective and does not follow Patent Office policy.

The Office Action states:

Determination of the scope and content of the prior art (MPEP 2141.01)

The Office Action stated: that Pye et al. teaches alkyl-methylsulfonyl ethanone substituted pyridine compounds of the same type recited in the claims; and see, for example, page 4, lines 5 to 25. This does not establish prima facie obviousness.

The Office Action dated:

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The Office Action stated that it is noted that Ar reads on phenyl or pyridinyl, substituted with C_{1-4} alkyl and R^1 reads on CH_3. This does not establish prima facie obviousness.

The Office Action stated:

Finding of prima facie obviousness—rational and motivation (MPEP 2142-2413)

The Office Action stated that it would have been obvious to one of ordinary skill in the art to modify Pye et al. due to the close structural relationship as the results would not have been unexpected. Applicants traverse this statement as being mere speculation and forbidden hindsight. Pages 2100-152 and 2100-153 of the M.P.E.P. (Rev. 3) requires first factually determining the

factors set out in the Graham decision before a prima facie showing of obviousness can be established.

This rejection should be withdrawn.

The Office Action stated that Claims 46 to 49, which process is neither taught nor suggested by the prior art, would be allowed if they did not depend from a rejected base claim and are, therefore, objected to. This objection should be withdrawn.

The Examiner has indicated allowability to Claims 46 to 49, subject only to clarifying the issue of non-allowability of Claim 45 to which said dependent and independent claims refer back to. In short, Claim 49 is a base claim comprising no referral to any other claim. Hence, such claim must be deemed allowed already. Claim 46 is a further base claim, only encompassing all features of Claim 45; however, incorrect the 103 rejection based on Claim 45 was, Claim 45 has only been rejected based on Amano et al. (which, as shown below, is not prior art to any of applicants' claims). Therefore, the objection of all Claims 45 to 48 (and 49, respectively) is moot, and all of the claims should be allowed.

Claims 21 to 44 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Bessard et al. (U.S. Patent No. 6,600,046 and/or Pye et al. (WO 98/47871) in view of Badia et al., [Bull. Soc. Chim. Belg., Vol. 98 no. 1 (1989)]. Applicants traverse this rejection.

Since Bessard et al. is not prior art, this obviousness rejection based on a combination of Bessard et al. and Badia et al. is fatally defective on its face.

Also since Bessard et al. is not prior art, this obviousness rejection based on a combination of Bessard et al., Pye et al. and Badia et al. is fatally defective on its face.

The Office Action stated that Bessard et al. and Pye et al. are applied as in the above rejections. Bessard et al. is not prior art. Pye et al., as shown above, has not been factually established to be a prima facie showing of obviousness. This obviousness rejection is defective.

The Office Action stated: that Bessard et al. and Pye et al. teach an analogous process using acetonitrile reactants of the type recited in the claims; and see the results and discussion. Applicants traverse this statement. Bessard et al. is not prior art. Pye et al. is in a combination rejection that is defective on its face.

The Office Action is to follow the Supreme Court's Graham decision in making determinations under Section 103(a). The obviousness rejection does not follow Office policy, hence the obviousness rejection is in error and should be withdrawn. The M.P.E.P., 2141.1 (Rev. 3), states:

> "Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103. As quoted above, the four factual inquiries enunciated therein as a background for determining obviousness are as follows:
>
> (A) Determining the scope and contents of the prior art;
>
> (B) Ascertaining the difference between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations." [Emphasis Supplied]

and also states:

"Accordingly, examiners should apply the test for patentability under 35 U.S.C. 103 set forth in *Graham*. See below for a detailed discussion of each of the *Graham* factual inquires."

The Section 103(a) rejection is incomplete and fails.

The Office Action states:

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The Office Action stated that Bessard et al. and Pye et al. differ in that they do not teach the process steps recited in the claims. Bessard et al. is not prior art. The Examiner only has forbidden hindsight as the basis for trying to combine Pye et al. and Badia et al. There is no reasonable suggestion of success of record of such combination (in the quest for applicants' claimed invention).

The Office Action stated that, however, Badia et al. teaches an analogous process using acetonitrile reactants of the type recited. Applicants disagree with this statement. The Office Action stated that, while Badia et al. teaches only analogous phenyl substituted reactants, it is noted that Pye et al. teaches phenyl and pyridine to be readily substituted in lieu of one another. There is no motivation in the prior art to combine such two references. The Office Action

stated see the page 4 definition for Ar. This does not cure the defects of this rejection.

Enclosed is a copy of Jerry March, Advanced Organic Chemistry, 1992 ed., sect. 6-49 (s. marked para. P 965, on bisulfite addition), 6-50 and esp. 6-12, which specifically relates to bisulfite addition to ketones or aldehydes. The skilled person's common and only knowledge related to conducting Strecker synthesis starting from ketone or aldehyde as an educt is eventually converting such aldehyde or ketone to its bisulfite adduct as an option. This is commensurate with Badia et al. (The attempted combination of Pye et al. and Badia et al. is hindsight.) According to the clear and present disclosure of Badia on page 79, middle section, the synthesis/provision of 2-(N,N-dimethylamino)-2-(2,3-dimethoxyphenyl)acetonitrile starts from 2,3-dimethoxybenzaldehyde. Upon work-up, apparently unreacted carbonyl compound is scavenged (and precipitated) by addition of bisulfite.

Hence, in short, nowhere does such combination of Pye et al. and Badia et al. teach all relevant features of Claim 22, namely, starting the synthetic route from an alkene, not a carbonyl compound, and obtaining the respective acetonitrile derivative in a single, one-pot reaction step without isolating a carbonyl compound ever by means of ozonolysis. This new, and surprising reaction short cut has not been described (or suggested) anywhere in the prior art, and is equally obtained even if there is isolating the bisulfite reaction products of Claims 45 as an intermediate. Ozonolysis requires, due to concomitantly formed peroxides, the presence of a reducing agent. By adding bisulfite to firstly-

formed ozonides as a mere reducing agent, it is newly possible to obtain bisulfite addition products directly from an alkene, in a single one-pot reaction step. Again, nowhere in the prior art has such method of obtaining bisulfite adducts been described (or suggested) before.

Therefore, applicant's claims as amended are certainly inventive and unobvious over the prior art. The alleged obvious combination of rejection documents fails to provide quite a number of features as claimed in Claim 22, starting with provision of the alkene educt on which Badia et al. is entirely tacit. Further, nowhere is there an allusion or suggestion of obtaining acetonitrile product synergistically in a single reaction step from alkene by means of ozonolyis to be found anywhere in Pye et al. and/or Badia et al.

The Office Action stated:

Finding of prima facie obviousness—rational and motivation (MPEP 2142-2413)

The Office Action stated that to modify the process of Badia et al. to include phenyl in lieu of pyridine would have been obvious to one of ordinary skill in the art as the use of somewhat different but otherwise analogous starting materials in an otherwise known process would not have been unexpected. Applicants traverse this statement. The Examiner has not factually determined in the record the level of ordinary skill therefore the Examiner does not know what is obvious to one of ordinary skill in the art, or anything at all about such person.

This rejection should be withdrawn.

Claim 45 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Amano et al. (U.S. Patent No. 6,642,387). Applicants traverse this rejection as Amano et al. is not prior art to applicants' claimed invention.

The earliest possible date that Amano et al. may have under Section 103(a)/Section 102(e) is February 16, 2000, that is the filing date of the Amano et al. International Application No. PCT/JP00/00861. Even this date is in doubt since the two priority applications are Japanese applications and the Examiner has not shown that such PCT application (filed in the Japanese PCT Office) was in English. As shown above, applications have benefit of three earlier foreign, PCT and domestic priority dates. Hence, Amano et al. is not prior art to Claim 45 or any other of applicants claims.

The Office Action stated:

Determination of the scope and content of the prior art (MPEP 2141.01)

The Office Action stated: that Amano et al. teaches pyridine sulfonic acid of the type recited in the claims; and see, for example, column 2, lines 15 to 45. Amano et al. is not prior art.

The Office Action stated:

Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)

The Office Action stated: that Amano et al. differs in that the 6-position substituent is not methyl; and that it is, e.g., methoxy. Amano et al. is not prior art.

The Office Action stated:

Finding of prima facie obviousness—rational and motivation (MPEP 2142-2413)

The Office Action stated that the claimed compounds in light of the teachings as a whole would have been obvious to one of ordinary skill in the art due to the otherwise close structural relationship. Amano et al. is not prior art.

This rejection should be withdrawn.

The Office Action stated that no claim is allowed. Applicants have shown that all of the pending claims should be allowed.

Reconsideration, reexamination and allowance of the claims are requested.

Respectfully submitted,

Date: 3/27/06

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P. 1825, PCT

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INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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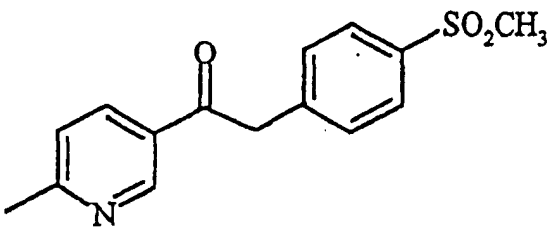
Veröffentlicht

Ohne internationalen Recherchenbericht und erneut zu veröffentlichen nach Erhalt des Berichts.

(54) Title: 1–(6– METHYLPYRIDINE– 3–YL)–2–[4– (METHYLSULFONYL) PHENYL] ETHANONE AND METHOD FOR ITS PREPARATION

(54) Bezeichnung: 1–(6– METHYLPYRIDIN– 3–YL)–2–[4– (METHYLSULFONYL) PHENYL] ETHANON UND VERFAHREN ZU SEINER HERSTELLUNG



(I)

(57) Abstract

The invention relates to a new starting product for the preparation of COX–2 inhibitors, notably the compound 1–(6– methylpyridine– 3–yl)–2–[(4– (methylsulfonyl) phenyl] ethanone of the formula (I), and to a method for producing same.

(57) Zusammenfassung

Es wird ein neues Ausgangsprodukt zur Herstellung von COX–2–Inhibitoren, die Verbindung 1–(6– Methylpyridin– 3–yl)–2–[4–(methylsulfonyl) phenyl]ethanon der Formel (I) sowie ein Verfahren zu dessen Herstellung beschrieben.

P00 2135 946

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FOURTH EDITION

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This book is dedicated to the nearly 20,000 scientists whose names are listed in the Author Index, and to my wife, Beverly, and our children, Gale, David, and June

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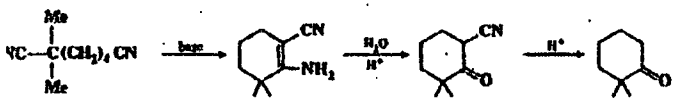
course, hydrolyzable (6-2), so β-keto nitriles can be prepared in this manner. The Thorpe reaction can be done internally, in which case it is called the *Thorpe–Ziegler reaction*.[692] This is a useful method for closing large rings. Yields are high for five- to eight-membered rings, fall off to about zero for rings of nine to thirteen members, but are high again for fourteen-membered and larger rings, if high-dilution techniques are employed. The product



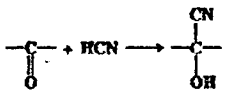
63

in the Thorpe–Ziegler reaction is not the imine, but the tautomeric enamine, e.g., 63; if desired this can be hydrolyzed to an α-cyano ketone (6-2), which can in turn be hydrolyzed and decarboxylated (6-5, 2-40). Other active-hydrogen compounds can also be added to nitriles.[693]

OS VI, 932.

J. Other Carbon Nucleophiles

6-49 The Formation of Cyanohydrins
O-Hydro-*C*-cyano-addition



The addition of HCN to aldehydes or ketones produces cyanohydrins.[694] This is an equilibrium reaction. For aldehydes and aliphatic ketones the equilibrium lies to the right; therefore the reaction is quite feasible, except with sterically hindered ketones such as diisopropyl ketone. However, ketones ArCOR give poor yields, and the reaction cannot be carried out with ArCOAr since the equilibrium lies too far to the left. With aromatic aldehydes the benzoin condensation (6-54) competes. With α,β-unsaturated aldehydes and ketones, 1,4-addition competes (5-25). Ketones of low reactivity, such as ArCOR, can be converted to cyanohydrins by treatment with diethylaluminum cyanide Et_2AlCN (see OS VI, 307) or, indirectly, with cyanotrimethylsilane Me_3SiCN[695] in the presence of a Lewis acid or base,[695a] followed by hydrolysis of the resulting O-trimethylsilyl cyanohydrin 64. When $TiCl_4$ is used,

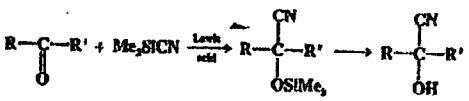
[692]For a monograph, see Taylor; McKillop *The Chemistry of Cyclic Enaminonitriles and ortho-Amino Nitriles*; Wiley: New York, 1970. For a review, see Schaefer; Bloomfield, *Org. React.* **1967**, *15*, 1–203.

[693]See for example, Josey *J. Org. Chem.* **1964**, *29*, 707; Barluenga; Fustero; Rubio; Gotor *Synthesis* **1977**, 780; Hiyama; Kobayashi *Tetrahedron Lett.* **1982**, *23*, 1597; Oswald; Bellmann; Ilnsch *Liebigs Ann. Chem.* **1984**, 1703; Page; van Niel; Westwood *J. Chem. Soc., Perkin Trans. 1* **1988**, 269.

[694]For reviews, see Fridrichsen, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 2; Wiley: New York, 1983, pp. 1345–1390; Friedrichs; Wallenfels, in Rappoport, Ref. 334, pp. 71–77.

[695]For reviews of Me_3SiCN and related compounds, see Rasmussen; Hellmann; Krepski *Adv. Silicon Chem.* **1991**, *1*, 65–187; Groutas; Felker *Synthesis* **1980**, 861–868. For procedures using Me_3SiCl and CN^- instead of Me_3SiCN, see Yonedn; Sanno; Hatusawa; Kurihara *Synthesis* **1978**, 1054; Sekiya *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3820.

[695a]Kobayashi; Tsuchiya; Mukaiyama *Chem. Lett.* **1991**, 537.



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the reaction between Me_3SiCN and aromatic aldehydes or ketones gives α-chloro nitriles Cl—CRR′—CN.[696]

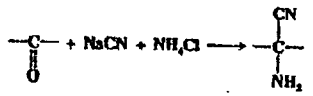
Frequently it is the bisulfite addition product that is treated with CN^-. This method is especially useful for aromatic aldehydes, since it avoids competition from the benzoin condensation. If desired, it is possible to hydrolyze the cyanohydrin in situ to the corresponding α-hydroxy acid. This reaction is important in the *Kiliani–Fischer* method of extending the carbon chain of a sugar.

The addition is nucleophilic and the actual nucleophile is CN^-, so the reaction rate is increased by the addition of base.[697] This was demonstrated by Lapworth in 1903, and consequently this was one of the first organic mechanisms to be known.[698]

The reaction has been carried out enantioselectively: optically active cyanohydrins were prepared with the aid of optically active catalysts.[699]

OS I, 336; II, 7, 29, 387; III, 436; IV, 58, 506; VI, 307; VII, 20, 381, 517, 521. For the reverse reaction, see OS III, 101.

6-50 The Strecker Synthesis
Cyano,amino-de-oxo-bisubstitution



α-Amino nitriles[700] can be prepared in one step by the treatment of an aldehyde or ketone with NaCN and NH_4Cl. This is called the *Strecker synthesis*;[700a] it is a special case of the Mannich reaction (6-16). Since the CN is easily hydrolyzed to the acid, this is a convenient method for the preparation of α-amino acids. The reaction has also been carried out with NH_3 + HCN and with NH_4CN. Salts of primary and secondary amines can be used instead of NH_4^+ to obtain N-substituted and N,N-disubstituted α-amino nitriles. Unlike 6-49, the Strecker synthesis is useful for aromatic as well as aliphatic ketones. As in 6-49, the Me_3SiCN method has been used; 64 is converted to the product with ammonia or an amine.[701]

OS I, 21, 355; III, 66, 84, 88, 275; IV, 274; V, 437; VI, 334.

[696]Kiyooka; Fujiyama; Kawaguchi *Chem. Lett.* **1984**, 1979.

[697]For a review, see Ogata; Kawasaki, in Zabicky *The Chemistry of the Carbonyl Group*, vol. 2, Wiley: New York, 1970, pp. 21–32. See also Okano; de Amaral; Cordes *J. Am. Chem. Soc.* **1976**, *98*, 4201; Ching; Kallen *J. Am. Chem. Soc.* **1978**, *100*, 6119.

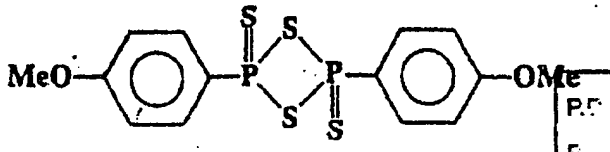
[698]Lapworth *J. Chem. Soc.* **1903**, *83*, 995.

[699]See Minamikawa; Hayakawa; Yamada; Iwasawa; Narasaka *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379; Jackson; Jayasekara; Matthews; Wilshire *Aust. J. Chem.* **1988**, *41*, 203; Gamez; Fernández; Gladysz *Tetrahedron Lett.* **1989**, *30*, 3031; Mori; Ikeda; Kinoshita; Inoue *Chem. Lett.* **1989**, 2119; Kobayashi; Tsuchiya; Mukaiyama *Chem. Lett.* **1991**, 541, and references cited in these papers.

[700]For a review of α-amino nitriles, see Shafran; Bakulev; Makrushin *Russ. Chem. Rev.* **1989**, *58*, 148–162.

[700a]For a review of asymmetric Strecker syntheses, see Williams *Synthesis of Optically Active α-Amino Acids*; Pergamon: Elmsford, NY, 1989, pp. 208–229.

[701]See Mai; Patil *Tetrahedron Lett.* **1984**, *25*, 4583; *Synth. Commun.* **1985**, *15*, 157.

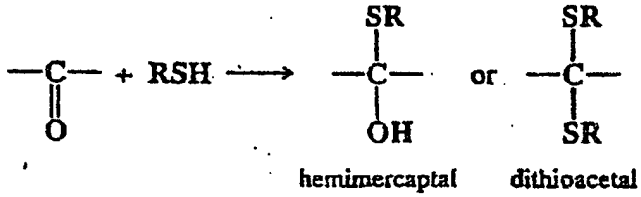


10

Cl_3 convert C=O groups of ketones, lactones, and lactams to C=S groups[119] and H_2S–Me_3SiCl–i-Pr_2NLi converts carboxylic esters to thiono esters.[120] Carboxylic acids RCOOH can be converted directly to dithiocarboxylic esters RCSSR′,[120a] in moderate yield, with P_4S_{10} and a primary alcohol R′OH.[121] Thioketones can also be prepared by treatment of ketones with P_4S_{10},[122] and from oximes or various types of hydrazone (overall conversion =N— → C=S).[123]

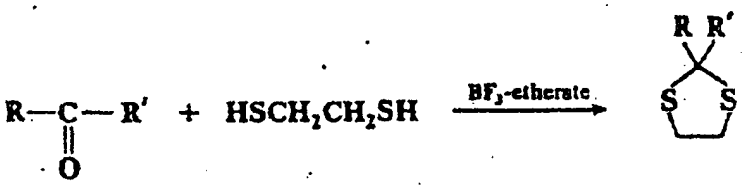
gem-Dithiols (8) are much more stable than the corresponding hydrates or α-hydroxy thiols.[124] They have been prepared by the treatment of ketones with H_2S under pressure[125] and under mild conditions with HCl as a catalyst.[126]

Thiols add to aldehydes and ketones to give hemimercaptals and dithioacetals. Hemimercaptals are ordinarily unstable,[127] though they are more stable than the corresponding



hemimercaptal dithioacetal

hemiacetals and can be isolated in certain cases.[128] Dithioacetals, like acetals, are stable in the presence of bases, except that a strong base can remove the aldehyde proton, if there one[129] (see 0-97). A common method for the protection of ketones involves treatment



[115]For reviews of this and related reagents, see Cava; Levinson *Tetrahedron* 1985, *41*, 5061-5087; Cherkasov; Ryrev; Pudovik *Tetrahedron* 1985, *41*, 2567-2624. For the preparation of 10, see Thomsen; Clausen; Scheibye; Vesson *Org. Synth. VII*, 372.

[116]Pedersen; Scheibye; Nilsson; Lawesson *Bull. Soc. Chim. Belg.* 1978, *87*, 223. For a study of the mechanism, Rauchfuss; Zank *Tetrahedron Lett.* 1986, *27*, 3445.

[117]For a review of thiono esters RC(=S)OR′, see Jones; Bradshaw *Chem. Rev.* 1984, *84*, 17-30.

[118]Scheibye; Pedersen; Lawesson *Bull. Soc. Chim. Belg.* 1978, *87*, 229; Ghattas; El-Khrisy; Lawesson *Sulfur Lett.* 2, *1*, 69; Yde; Yousif; Pedersen; Thomsen; Lawesson *Tetrahedron* 1984, *40*, 2047; Thomsen et al., Ref. 115.

[119]Steliou; Mrani *J. Am. Chem. Soc.* 1982, *104*, 3104.

[120]Corey; Wright *Tetrahedron Lett.* 1984, *25*, 2639.

[120a]For a review of dithiocarboxylic esters, see Kato; Ishida *Sulfur Rep.* 1988, *8*, 155-323.

[121]Davy; Metzner *Chem. Ind. (London)* 1985, 824.

[122]See, for example, Scheeren; Ooms; Nivard *Synthesis* 1973, 149.

[123]See for example, Kimura; Niwa; Motoki *Bull. Chem. Soc. Jpn.* 1977, *50*, 2751; de Mayo; Petrašiūnas; Weedon *Tetrahedron Lett.* 1978, 4621; Okazaki; Inoue; Inamoto *Tetrahedron Lett.* 1979, 3673.

[124]For a review of the preparation of *gem*-dithiols, see Mayer; Hiller; Nitzschke; Jentzsch *Angew. Chem. Int. Ed. Engl.* 1963, *2*, 370-373 [*Angew. Chem.* 75, 1011-1014].

[125]Cairns; Evans; Larchar; McKusick *J. Am. Chem. Soc.* 1952, *74*, 3982.

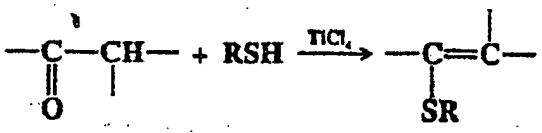
[126]Ref. 109; Demuynck; Vialle *Bull. Soc. Chim. Fr.* 1967, 1213.

[127]See, for example, Fournier; Lamaty; Nata; Roque *Tetrahedron* 1975, *31*, 809.

[128]For example, see Field; Sweetman *J. Org. Chem.* 1960, *34*, 1700.

dithioketal can be desulfurized with Raney nickel (4-36), giving the overall conversion C=O → CH_2. Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of $TiCl_4$,[131] $SiCl_4$,[132] or polyphosphoric acid trimethylsilyl ester;[133] with a disulfide RSSR (R = alkyl or aryl),[134] or with methylthiotrimethylsilane $MeSSiMe_3$.[135]

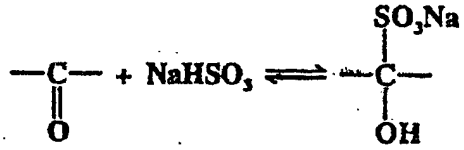
If an aldehyde or ketone possesses an α hydrogen, it can be converted to the corresponding enol thioether by treatment with a thiol in the presence of $TiCl_4$:[136]



Aldehydes and ketones have been converted to sulfides by treatment with thiols and pyridine–borane, RCOR′ + R″SH $\xrightarrow{BH_3}$ RR′CHSR″,[137] in a reductive alkylation reaction, analogous to 6-7.

OS II, 610; IV, 927; VI, 109; VII, 124, 372. Also see OS III, 332; IV, 967; V, 780; VI, 556; 65, 215.

6-12 Formation of Bisulfite Addition Products
O-Hydro-*C*-sulfonato-addition



Bisulfite addition products are formed from aldehydes, methyl ketones, cyclic ketones (generally seven-membered and smaller rings), α-keto esters, and isocyanates, upon treatment with sodium bisulfite. Most other ketones do not undergo the reaction, probably for steric reasons. The reaction is reversible (by treatment of the addition product with either acid or base[138])[139] and is useful for the purification of the starting compounds, since the addition products are soluble in water and many of the impurities are not.[140]

OS I, 241, 336; III, 438; IV, 903; V, 437.

[130]For a review, see Olsen; Currie, in Patai *The Chemistry of the Thiol Group*, pt. 2; Wiley: New York, 1974, pp. 521-532.
[131]Kumar; Dev *Tetrahderon Lett.* 1983, *24*, 1289.
[132]Ku; Oh *Synth. Commun.* 1989, 433.
[133]Kakimoto; Seri; Imai *Synthesis* 1987, 164.
[134]Tazaki; Takagi *Chem. Lett.* 1979, 767.
[135]Evans; Grimm; Truesdale *J. Am. Chem. Soc.* 1975, *97*, 3229.
[136]Mukaiyama; Saigo *Chem. Lett.* 1973, 479.
[137]Kikugawa *Chem. Lett.* 1981, 1157.
[138]For cleavage with ion-exchange resins, see Khusid; Chizhova *J. Org. Chem. USSR* 1985, *21*, 37.
[139]For a discussion of the mechanism, see Young; Jencks *J. Am. Chem. Soc.* 1978, *100*, 1228.
[140]The reaction has also been used to protect an aldehyde group in the presence of a keto group: Chihara; Wakabayashi; Taya *Chem. Lett.* 1981, 1657.